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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/524,295	PRINZENBERG ET AL.	
	Examiner	Art Unit	
	Sarae Bausch, PhD	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *1-4 and 19-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 February 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *02/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to applicants correspondence mailed 08/15/2008. The amendment to the claims mailed 04/18/2008 has been entered

Election/Restrictions

2. Applicant's election of group II in the reply filed on 04/18/2008 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

3. Claims 1-4 and 19-21 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 04/18/2008.

4. It is noted that applicant's indicate that claim 18 is withdrawn and non-elected however claim 18 was placed in group II in the restriction mailed 03/20/2008 and is not independent or distinct from the elected invention, therefore claim 18 is under examination.

Drawings

5. The drawings are acceptable.

Sequence Rules

6. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825. For example, claims 2 and 21 have sequences that do not contain sequence identifiers. Although claims 2 and 21 are withdrawn the claims are pending and thus must comply with the sequence rules. Additionally, figure 2 contains sequences that do not contain sequence identifies. The amendment to the drawings does not correct this deficiency as the amendment mailed 08/15/2008 indicates SEQ ID No 5 however each of the sequences in figure 2 are different, each allele has a different sequence and thus not all of the sequences depicted in figure 2 have the sequence of SEQ ID NO 5. Applicant is required to provide sequence identifiers for each of the sequences listed in figure 2.

Claim Objections

7. Claims 5-18 objected to because of the following informalities: claim 5 is not grammatically correct. Appropriate correction is required. Claim 5 does not contain the appropriate verb tense, proper punctuation, step (d) begins with a capitol letter, and the claim does not recite "and" between the penultimate and ultimate step. For example claim 5 should

recite A method to determine the presence of an allele in the 5'-flanking region of the αs1 casein gene, comprising a). providing source material of an organism to be examined, b) isolating genetic material from the source material, c). isolating a fragment of the 5' region of the αs1 casein gene, and d) determining the presence of an allele in the fragment of the 5' region of the αs1 casein gene.

8. Claim 18 objected to because of the following informalities: claim 18 depends from a withdrawn claim. Appropriate correction is required.

Claim Rejections - 35 USC § 112- Second Paragraph

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 5-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a). Claim 5 recites the limitation ""the source material" in step (a), "the genetic material" in step (b), and "the marker fragment", "the marker sequence" and "the 5' region" in line 1 and step (c). There is insufficient antecedent basis for these limitations in the claim. None of the steps preceding recite any source material, genetic material, marker fragments or sequences, or 5' region and thus it is unclear which is "the" source material, genetic material, marker fragment, marker sequence, and 5' region refers to the in claim.

(b). Claim 5 recites "the fragment 1 to 655 of the marker sequence out of the αs1 casein gene". This phrase renders the claim vague and indefinite as the position is arbitrary without a

point of reference. It is unclear if fragment 1 to 655 references a starting position within the isolated marker sequence, a first position relative to a position of the gene, the coding sequence where position 1 corresponds to position 1 of the first codon, or a position relative a region of the promoter region of the gene. Thus, the metes and bounds of the claim are indefinite.

(c). Claim 6-9 recites the limitation "the utilization of source material" in 1. There is insufficient antecedent basis for this limitation in the claim. None of the steps preceding recite a process step of utilizing source material and therefore it is unclear which step of claim 5 claim 6 intends to limit.

11. Claim 14-18 provides for the utilization of the procedure according to claim 5 fro milk production traits (claim 14), select organisms which carry allelic state (claim 15), in breeding programs (claim 16), selection of increased milk protein yield (claim 17) and use of a marker according to patent claim 1 for genome analysis (claim 18), but, since the claims do not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 14-18 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112-Description

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 5-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

> Applicant is referred to the revised training materials on written description available at www.uspto.gov/web/menu/written.pdf. Of particular relevance to the rejected claims 5-18 are examples 7 and 17 on page 25-28 and 58-60 of the training materials addressing methods claimed encompassing alleles and functional limitations.

The rejected claims are broadly drawn to a procedure to determine an allelic state of the 5' flanking region of the αs1 casein gene by isolation of genetic material, target isolation or enrichment of the marker fragment of the 5' flanking region of the αs1 casein gene or a sequence which contains portion of the marker sequence, preferable the fragment 1 to 655 of the marker sequence out of the αs1 casein gene, and proof of the allelic state in the isolated or enriched sequence fragment. The claims are further drawn to source material from an animal or genetically modified organism. Additional claims are drawn to detection of one or more allelic states of the marker sequence of the αs1 casein gene, and use of the claimed method for examination of animal milk production trials, selection of organisms that carry allelic state, selection of increased milk yields, and genome analysis. The claims are broadly drawn to

methods comprising the detection of a variety of nucleic acids, including any polymorphic variant in any region of the αs1 casein gene and any size region that is a 5' flanking region of the αs1 casein gene in any organism.

When the claims are analyzed in light of the specification, the instant invention encompasses methods comprising the analysis and detection of an enormous and wide variety of nucleic acid sequences. The claims are broadly drawn to a method that encompass a plurality of nucleic acids an extremely large genus of polymorphic variants of in a region of any size that is 5' flanking region of the αs1 casein gene with any nucleotide content (A or G or C or T) or any type of allele (insertion, deletion, etc) at any position within in a region that is 5' flanking of the αs1 casein gene in any species. Thus the claims encompass the detection of any of the many different nucleic acids and wherein the nucleic acid sequence is correlated with an association of milk production or selection process in any species. Nucleic acids of such a large genus have not been taught by the specification.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. The instant specification provides the sequence of SEQ ID No. 5 and lists alleles 1-4 (that do not have sequence identifiers) which corresponds to a 5' flanking region of the αs1 casein gene, of which none of the variants show an association with milk production or breeding (see table 2) as the data does not provide for statistical analysis of genotypes. Additionally, although alleles 1-4 are printed in figure 2, it is unclear how these alleles differ from the wild type sequence of a 5' flanking region of the αs1 casein gene in bovine, much less any species. Additionally the specification does not define what is encompassed by the 5' region

of the αs1 casein gene and thus the 5' region of the αs1 casein gene encompasses varying amount of nucleotides and specification does not provide a representative number of marker sequences or allelic states for this non-limiting region in any species.

Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e. other than nucleotide sequence, gene name, and specific polymorphic position), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, the specification provides only the sequence of SEQ ID NO 5 and the sequence of alleles 1-4, which appears to be an undefined region of the 5' region the αs1 casein gene sequences in bovine. The specification does not provide any characteristics that would allow one to identify any particular portions or fragments or variants of the disclosed sequence that would allow for the detection of an allelic state in any species, as the specification does not provide for the wild type sequence in any species, as well as determine milk production traits and breeding in any species based on the detection of the non-disclosed 5' flanking region of the αs1 casein gene or marker sequence. Furthermore, the art discloses that there are 91 SNPs known for the human αs1 casein gene (see GeneCard, page 8), the specification does not disclose analysis of any of these allelic states of the αs1 casein gene. Additionally, the art teaches that not all alleles of the αs1 casein gene are not associated with milk production in the in all species. For example, Ordas (Small Ruminant Research, 2001, vol. 41, pp. 71-75) teaches that no ovine casein variant has been determined that accurately defines incidence of selection based on milk production and that the evolutionary meaning of polymorphism still has not been clarified and the controversy between selections and neutralist continues (see pg. 74, 1st column, 2nd full para).

Applicants' attention is directed to the decision in *In re Shokal*, 113 USPQ 283 (CCPA 1957) wherein is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. In re Soll, 25 C.C.P.A. (Patents) 1309, 97 F.2d 623, 38 USPQ 189; In re Wahlforss et al., 28 C.C.P.A. (Patents) 867, 117 F.2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

In the instant application, because of the lack of any analysis regarding any allelic state or marker fragment of a 5' region of the αs1 casein gene other than alleles 1-4, one of skill in the art cannot envision the detailed chemical structure of the nucleic acid encompassed by the claimed methods, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that such nucleic acids are part of the invention and reference to a potential method for identification. The particular nucleic acids are themselves required.

In conclusion, the limited information provided regarding the nucleic acids of the claimed methods is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of a method for identifying an allelic state of a 5' flanking region of the αs1 casein gene much less determination of the allelic state with milk production or breeding in any species.

Thus, having considered the breadth of the claims and the provisions of the specification, it is concluded that the specification does not provide adequate written description for the claims.

Claim Rejections - 35 USC § 112-Scope of Enablement

14. Claims 5-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method to determine the presence of an allele in the 5'-flanking region of the αs1 casein gene comprising SEQ ID NO 3, comprising a). providing biological material of an organism to be examined, b) isolating genetic material from the source material, c). isolating a fragment of the 5' flanking region of the αs1 casein gene comprising SEQ ID NO 3, and d) determining the presence of an allele in the 5' flanking region of the αs1 casein gene comprising SEQ ID NO 3, does not reasonably provide enablement for the claims as written. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and the breadth of the claims

The claims are drawn to a procedure to determine an allelic state of the 5' flanking region of the αs1 casein gene by isolation of genetic material, target isolation or enrichment of the

marker fragment of the 5' region of the αs1 casein gene or a sequence which contains portion of the marker sequence, preferable the fragment 1 to 655 of the marker sequence out of the αs1 casein gene, and proof of the allelic state in the isolated or enriched sequence fragment. The claims are further drawn to source material from an animal or genetically modified organism. Additional claims are drawn to detection of one or more allelic states of the marker sequence of the αs1 casein gene, and use of the claimed method for examination of animal milk production trials, selection of organisms that carry allelic state, selection of increased milk yields, and genome analysis.

The rejected claims encompass analysis of any organism, including human and non-human. The rejected claims encompass any type of allele or allelic state of a non-defined region that is a 5' region of the αs1 casein gene. The rejection claims encompass any type of milk trait, selection or breeding trait.

The nature of the claims requires knowledge of a correlation between detection of an allelic state of a 5' region of the αs1 casein gene and association with milk trait or selection.

The invention is in a class of inventions which the CAFC has characterized as "the unpredictably arts such as chemistry and biology" (Mycolgen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)).

Guidance in the Specification and Working Examples

The specification asserts a method to classify cattle independent of age and lactation by determination of an allelic state of genetic markers at the 5' flanking region of the αs1 casein gene (CSN1S1) and the casein gene (see pg 7 lines 8-14). The specification teaches that 4 alleles were detected through single strand conformation polymorphism analysis. The

specification teaches that alleles 1, 3, and 4 differ from allele 2 (which appears to be the wild type sequence however the specification never teaches the wild type sequence) by various substitution and deletions (see pg. 8, lines 26-35).

The specification teaches the sequence fragment is enhanced by PCR using the combination of primer 1 with primer 2 or primer 1 with primer 3 (see pg. 11, lines 5-20). However claim 11 requires PCR with primer 1 and primer 2 or primer 2 and primer 3 however the specification does not analyze any allelic state with the combination of primer 2 and primer 3 and it is unclear what would be determined using this specified primer combination.

The specification teaches utilizes routine sequence methods to determine the allelic state of the 5' flanking region of the αs1 casein gene, for example PCR, array analysis, sequencing (see pg. 12). The specification further teaches that in the case of sequencing a comparison of nucleotide sequence 1, 2, 3, and 4 of figure 2 (alleles 1-4) must be carried out in order to establish an analogical correlation between alleles.

The specification demonstrates working examples of classifying milk production traits through determination of allelic state of markers. The specification teaches analysis of cattle blood and isolation of genetic material followed by PCR amplification and gel analysis (see pg. 15). The specification teaches 83 cattle of 6 different breeds were analyzed (See pg. 16) and teaches analysis of 503 cows of German Holstein (see pg. 16-17). The specification asserts that allele 2 represents the most frequent allele followed by allele 3 and allele 1 and 4 (see pg. 17, lines 1-15), however the specification does not teach any statistical analysis of the genotype frequencies, for example there is no analysis of 95% confidence levels or p values associated with the data.

The specification further teaches analysis of 729 bulls and 9 half sib families of German Holstein and Simmental were genotypes with marker CSN1S and teaches the genotypes in table 2. However table 2 merely provides the number of bulls with the genotype and does not provide any statistical analysis for the probability of the genotype associated with a family or a breed. The specification further teaches analysis of marker CSN1S1 on milk yield, protein and fat yield, and protein and fat percentage (see pg. 20, lines 1-15). The specification asserts that table 3 shoes the effect of CSN1S1 on breeding values for milk product traits indicating the probability of error for these effects. However it is unclear what the p value analysis is for, as the table does not provide analysis of which genotype is associated with a specific breeding value. Does this p value represent an association of all the genotypes combined, one specific genotype, one specific combination of genotypes, etc. The specification does asserts that on average bulls with genotype 12 have the highest breeding value for milk whereas the highest breeding value for protein is genotype 24, however no p values associated with these genotypes was analyzed. Table 4 does present lest square means and standard errors however this does not provide probability of error such that a specific genotype would be predictably associated with specific breeding value. The specification further asserts that a comparison of the LS means and traits were carried out for all groups of genotypes and within each individual family and is graphically illustrated in figure 5. However, figure 5 does not provide statistical analysis and values that would predictably correlate genotypes within individual families and traits.

The specification does not teach any analysis of any organism other than cattle. The specification does not teach analysis of any genetically modified organism. The specification does not teach analysis of any other region of 5' flanking region of CNS1S other than SEQ ID

NO 3 in cattle. The specification does not teach any analysis of any type of selection or milk trait other than fat and protein content. Furthermore, the specification does not provide any guidance on how alleles 1-4 differ from the wild type sequence of a 5' flanking region of CNS1S. The specification does not teach a statistically significant association of milk or breeding trait in any cattle, much less any organism with any allelic state of CNS1S. The specification does not teach any selection of any organism based on increased milk protein yields.

The following is unclear from the teaching in the specification. The specification does not teach which polymorphism or allelic states of any 5' flanking region of CNS1S gene is predictably correlative to determining milk or breeding selection in any cattle, much less any other animal, such as pig, goat, sheep, etc. The specification does not teach which genotypes should be selected, which genotypes produce increase milk protein, or which genotypes would be involved in any breeding programs. The specification does not present statistical analysis of the genotype frequencies of different cattle breed, different milk and breeding traits within the different breeds, much less analysis of genotype association of milk and breeding traits in Holstein cattle. The specification does not define the 5' flanking region of CSN1S other than amplification and resulting SEQ ID NO 3, or which sequence is the wild type to therefore be able to determine alleles.

Level of skill in the art, the unpredictability of the art and the state of the prior art

While the state of the art and level of skill in the art with regard to detection of a polymorphism in a known gene sequence is high, the level of unpredictability in associating any particular polymorphism with a phenotype is even higher. The level of unpredictability is demonstrated by the prior art, the post filing art, and the instant specification.

It is unpredictable as to whether or not an allelic state of a 5' flanking region of the αs1 casein gene sequence exists in any non-bovine organisms, and whether or not detection of an allelic state in such a sequence in any other organism would be predictive of selection or milk traits. For example, Mummidi et al. (2000). Mummidi et al. teaches the sequence analysis of the CC chemokine receptor 5 (CCR5) gene in humans and non-primates. Notably, the reference teaches that the substantial interspecies sequence variation is observed for the cis-regulatory regions of the CCR5 gene (p. 18949, right column, 1st full paragraph). Thus it is entirely unpredictable as to whether or not any allelic states would be associated with selection or milk production.

Because the claims are drawn to methods that encompass the analysis of any allelic state of a 5' flanking region of the αs1 casein gene, it is relevant to note that there are multiple polymorphic positions identified in human αs1 casein gene, much less any other organism. A Gene Card search of human αs1 casein gene indicates that there are 91 SNPs (see page 8 of Gene Card). The instant specification does not teach any association of these 91 polymorphisms with milk production.

Additionally, the prior art teaches that there are many parameters that need to be evaluated prior to using a genetic test to determine a phenotype association and that these parameters yield gaps in information that are needed to complete a thorough screening of a genetic test. Post filing art, Kroese et al. (Genetics in Medicine, vol 6 (2004), p. 475-480) teach genetic tests are heterogeneous in nature and the exact characteristics of a particular genetic test to be evaluated must be tightly defined. Kroese et al. teach that a particular genetic condition may be caused by more than one gene and these variations may be due to deletions and

insertions not detected by routine sequence methods. (see page 476, 2nd column, last paragraph). Kroese et al. teach that genetic test is shorthand to describe a test to detect a particular genetic variant for a particular disease in a particular population and for a particular purpose and that it should not be assumed that once the characteristics of a genetic test are evaluated for one of these reasons that the evaluation will hold or be useful for other purposes and all measures of the test performance should be presented with their 95% confidence intervals (see page 477, 1st column, 1st and 2nd full paragraph). Kroese et al. teach that the limitations of our genetic knowledge and technical abilities means that for the moment there are likely to be gaps in the information needed to complete a thorough evaluation of many genetic tests (see page 479, 2nd column, last paragraph).

Furthermore, Ionnidis (Plost Med, 2005, 2(8):e124) teach that most published research findings are false. Ionnidis et al. teach that ill-founded strategy of claiming conclusive research finding solely on the basis of a single study assed by formal statistical significance represented and summarized by p values (see pg. 0696, 2nd column, 1st full para.) Ionnidis et al. teach that research findings are likely to be true that in fields that undertake large studies, such as randomized controlled trials (several thousand subjects randomized) than in small studies such as sample sizes 100 fold or smaller (see pg. 0697, 3rd column, 2nd full para.) Ionnidis et al. teaches that what matters is the totality of evidence and that statistical significance of a single study only gives a partial picture (see pg. 0701, 1st column). Additionally, Hattersley et al. (Lancet, 2005, vol 366, pp. 1315-1323) teaches that the key quality in an association study is sample size (see page 1318, 2nd column, 1st full paragraph). Hattersley et al. teach that sample sizes of thousands are needed to detect variants that are common but have low relative risk and teach that allelic

odds ratio of 1.1 to 2.0 requires the number of controls to be in thousands (see page 1318, 2nd column, 1st full paragraph and table 3). Hattersley et al. teach that apparent studies in identifying interesting associations with studies much smaller than implied by table 3 (in the thousands) might suggest that calculations are too pessimistic and small initial studies rarely find the correct result and even when they do they are likely to overestimate the true effect size (see page 1318, 1st column, 1st full paragraph). Hattersley et al. further teaches that emphasis has been on the need for greater stringency in the association studies in order to prove a given association and suggest a p value of $5x10^{-8}$, however arguments from Bayesian perspective suggest that $5x10^{-5}$ should be sufficient to constrain the false discovery rate. It is further relevant to point out that Hegele (2002) teaches the general unpredictability in associating any genotype with a phenotype. Hegele teaches that often initial reports of an association are followed by reports of non-replication and refutation (p.1058, right col., lns.24-30). Hegele provides a table indicating some desirable attributes for genetic association studies (p.1060), and includes choosing an appropriate significance threshold (see 'Minimized type 1 error (FP)') and replication of results in independent samples (see 'Replication'). Additionally, Hegele teaches the desirability of a likely functional consequence predicted by a known or putative functional domain.

Furthermore, the post filing art by Ordas (Small Ruminant Research, 2001, vol. 41, pp. 71-75) teaches that no ovine casein variant has been determined that accurately defines incidence of selection based on milk production and that the evolutionary meaning of polymorphism still has not been clarified and the controversy between selectionist and neutralist continues (see pg. 74, 1st column, 2nd full para). Thus, Ordas teaches that polymorphisms in the αs1 casein gene are not predictably associated with milk production in all organisms.

Additionally, applicants own post filing art teaches the unpredictability in associating alleles in the 5' flanking region of the αs1 casein gene with milk production. Prinzenberg et al. (Livestock Production Science 2005, 98, pp. 155-160) teaches 5 known alleles in the 5' flanking region of αs1 casein gene (see pg. 155, last para con't to page 156). Prinzenburg teach analysis of 14 breeds of cattle for genotyping studies and analysis of traits. Prinzenburg teaches that allele 5 was not found (see pg. 157, last para) and allele 2 is probably the wild type sequence (see pg. 158, 1st column, 1st full para). Prinzenburg teaches that no significant effects were found for milking speed, temperature, composite relative breeding value body conformation (See pg. 158, 2nd column, 2nd full para and table 2). Prinzenburg teaches the genotype only provided significant association with udder shape and udder health (See pg. 158, 2nd column, 3rd full para). Prinzenberg teaches allele frequencies demonstrated a high variability (see pg. 159, 2nd column, last para). Prinzenberg teaches that alleles require monitoring if any gene assisted selection is to be implemented and further teaches that for all other breeds, these associations need to be evaluated before considering CN1S1-5' as marker in selection programs. Therefore, Prinzenburg teaches there is significant unpredictability of associating any polymorphism or allelic state of the 5' flanking region of αs1 casein gene with any type of milk trait or selection process.

Based on the data presented in the specification and the prior art teachings, it is unpredictable to correlate any polymorphism within 5' flanking region of the αs1 casein gene with any selection or any milk trait in any organism, as the specification does not teach a large confidence levels and statistical analysis with a p value less than .05 for a representative number of polymorphisms within 5' flanking region of the αs1 casein gene in a representative number of organisms, including genetically modified organisms. The specification only teaches a large

sample size for genotyping of Holstein cattle, however the specification does not provide statistical analysis for milk trait or selection process for each of the different genotypes, much less teach analysis of alleles in different organisms.

Quantity of Experimentation

Given the lack of guidance in the specification with regard to association of any polymorphism in 5' flanking region of the αs1 casein gene in "any" species with milk traits and selection the quantity of experimentation in this area is extremely large. The skilled artisan would have to perform an extremely large study and include different populations in different species for each of the polymorphisms in the 5' flanking region of the αs1 casein gene to determine if in fact there was either an association between the polymorphism and selection or milk traits, in any organism, human, dog, cat, rat, sheep, goat, cattle, etc. The results of such a study are unpredictable as evidence by the post filing art (which reflects the current state of the art) and the teachings in the specification. In the instant case, it would be unpredictable as to whether or not polymorphisms of 5' flanking region would be responsible for determining the predisposition to milk trait or selection process in any organism. In order to practice the invention as broadly as it is claimed, the skilled artisan would have to perform an extremely large amount of trial and error analysis in a large study to determine if such allelic states would be predictable determine milk or selection trait in any organism. Given the lack of guidance in the specification and the post filing art with respect to accurately testing genetic phenotypes, such analysis is replete with unpredictable experimentation and is considered undue.

Claim Rejections - 35 USC § 102

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

16. Claims 5-10, 12-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Schild et al. (1996, cited on IDS).

With regard to claim 5-8, Schild et al. teach selecting animals followed by PCR amplification of αs1 casein gene of genomic DNA (see materials and method, pg. 887) (providing source material, isolation of genetic material, enrichment of marker fragment). Schild et al. teach sequence of the 5' region of 13 cows and teach 17 variable sites (see figure 1) (proof of allelic state in isolated or enriched sequence fragment) (claim 2). Schild et al. teach 34 variable sites within the cows.

With regard to claim 8, Schild et al. teach 17 variable sites within the cows, thus Schild teach utilization of source material coming from a genetically modified organism which contains the marker fragment (allele present in different cows) and Schild et al. teach analysis by PCR thus Schild teaches using the source material of the mutations that are present for genotyping analysis (claim 8).

With regard to claim 9, Schild et al. teach PCR amplification of genomic DNA, thus Schild teach utilization of genetic material containing genomic DNA (see material and method, pg. 887).

With regard to claim 10, Schild et al. teach PCR amplification (see material and method, pg. 887).

With regard to claim 12-13, Schild et al. teach DNA sequencing to determine 17 variations in the 5' flanking region of αs1 casein gene (see figure 1).

With regard to claim 15, Schild et al. teach selection of animals for genotyping and presence of genotype with breed (see pg. 887 and table 3).

With regard to claim 18, Schild et al. teach genome analysis of αs1 casein gene to determine 17 variations in the 5' flanking region of the αs1 casein gene (see figure 1 and table 3).

It is noted that with regard to claim 14-18, the claims recite an intended use of the method/product and the claims do not recite how the recited use relates to or alters any of the active process steps. Therefore, Schild anticipates the claimed methods, which merely require the steps recited in claim 5 or the nucleic acid recited in claim 1.

17. Claims 5-10, 12- 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Koczan (1993, cited on IDS).

Koczan et al. teach isolation of genomic DNA (claim 7-9) from cattle (claim 6) (see source/description, pg. 74). Koczan et al. teach PCR amplification of genomic DNA followed by RFLP analysis (claim 10, 12) (see PCR pg 74). Koczan et al. teach detection of an allele at -175 in the 5' flanking region of αs1 casein gene (claim 13, 15 and 18). Thus Koczan teaches isolation of source material, genetic material, enrich of genetic material followed by proof of genetic material (RFLP analysis). Additionally, Koczan et al. teach determining allelic states by detecting the allele at position -175, as well as selecting animals that carry the allele, and analysis of 5' flanking region of αs1 casein gene for genetic mapping and linkage analysis.

It is noted that with regard to claim 14-18, the claims recite an intended use of the method/product and the claims do not recite how the recited use relates to or alters any of the active process steps. Therefore, Koczan anticipates the claimed methods, which merely require the steps recited in claim 5 or the nucleic acid recited in claim 1.

18. Claims 5-8 and 12-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Hang (1983, cited on IDS).

With regard to claim 5 and 12, Hang et al. teach isolating milk sample from individual cows. Hang et al. teach analysis of samples by gel electrophoresis (see materials and methods, pg. 835) (claim 12). Hang et al. teach analysis of variant frequencies of A, B, and C. Therefore, Hang et al. teach providing source material, isolating genetic material, targeted isolation of genetic material, which contains portion of a marker sequence, and proof of allelic state. It is noted that claim 5 merely requires isolation of a marker fragment at the 5' region of the αs1 casein gene or of a sequence which contains portions of the marker sequence and thus the marker sequence can comprise portions of the coding sequence, such as the 5' coding region. Additionally, SEQ ID NO 3 comprises a portion of the 5' coding region which encompasses a marker sequence taught in the specification.

With regard to claim 6-8, Hang et al. teach isolation of milk sample from cattle and analysis of allelic variants (see table 1 and materials and methods pg. 835).

With regard to claim 13, 15, and 18, Hang et al. teach analysis of allele presence and frequencies (see table 1). Thus, Hang teach use of selecting cows that comprise the allelic state and genome analysis

With regard to claim 14, 16-17, Hang et al. teach analysis of allele presence and milk protein, lactation, and fat yield (See figure 1 and figure 2). Thus, Hang et al. teach analysis of examining milk traits, selection for breeding and milk.

It is noted that with regard to claim 14-18, the claims recite an intended use of the method/product and the claims do not recite how the recited use relates to or alters any of the active process steps. Therefore, Hang anticipates the claimed methods, which merely require the steps recited in claim 5 or the nucleic acid recited in claim 1.

19. Claims 5-10, 12- 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Schlee (1992, cited on IDS) as evidence by Koczan (1993, cited on IDS).

With regard to claim 5-7, 9-10, 12, Schlee et al. teach isolation of genomic DNA (claim 9) from blood samples (claim 7) from cattle (claim 6) and allele specific PCR (claim 10, 12)(providing source material, isolation of genomic DNA, and enrichment of DNA) (see pg. 316, last para). Schlee et al. teach analysis by gel electrophoresis (see fig 1).

With regard to claim 8 and 13, Schlee et al. teach detection of B and C alleles (detection of one or more alleles) in cattle therefore Schlee et al. teach using source material for PCR amplification from a genetically modified organism (see figure 1).

With regard to claim 15-16, and 18, Schlee et al. teach genotyping 60 cows and teach analysis for early selection of breeding animals which carry the desired milk protein variants (see pg. 318, last para).

Additionally, it is noted that Koczan teaches that allele B of αs1 casein gene also contains an allele at -175, within the 5' flanking region of the αs1 casein gene (see pg. 74). Therefore

analysis of the B allele will necessarily result in isolation and proof of an allele in the 5' flanking region of the αs1 casein gene.

Additionally, the claims do not require a specified region of the 5' region of the αs1 casein gene and therefore alleles that encompass any 5' portion of the αs1 casein gene would be encompassed by the claims and therefore allele B and C, as taught by Schlee encompass a 5' region of the αs1 casein gene.

Furthermore, it is noted that with regard to claim 14-18, the claims recite an intended use of the method/product and the claims do not recite how the recited use relates to or alters any of the active process steps. Therefore, Schlee anticipates the claimed methods, which merely require the steps recited in claim 5 or the nucleic acid recited in claim 1.

Claim Rejections - 35 USC § 103

20. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

21. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

22. Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Schiled (1996) in view of Koczan (1993), Hogan et al. (US Pat. 5,541,308, July 30, 1996), and Buck et al (Biotechniques (1999) 27(3):528-536).

Schild et al. teach selecting animals followed by PCR amplification of αs1 casein gene of genomic DNA (see materials and method, pg. 887) (providing source material, isolation of genetic material, enrichment of marker fragment). Schild et al. teach sequence of the 5' region of 13 cows and teach 17 variable sites (see figure 1) (proof of allelic state in isolated or enriched sequence fragment) (claim 2). Schild et al. teach 34 variable sites within the cows are analyzed. Schild et al. does not teach primers 1 and 2 or 2 and 3.

However, Koczan et al. teach isolation of genomic DNA (claim 7-9) from cattle (claim 6) (see source/description, pg. 74). Koczan et al. teach PCR amplification of genomic DNA followed by RFLP analysis (see PCR pg 74). Koczan et al. teach detection of an allele at -175 in the 5' flanking region of αs1 casein gene using primer 2, SEQ ID NO 2.

Hogan et al. (herein referred to as Hogan) teaches the use of specific primers col. 6-7, lines 50-67, lines 1-12, and furthermore provides specific guidance for the selection of primers,

> "Once the variable regions are identified, the sequences are aligned to reveal areas of maximum homology or 'match'. At this point, the sequences are examined to identify potential probe regions. Two important objectives in designing a probe are to maximize homology to the target sequence(s) (greater than 90% homology is recommended) and to minimize homology to non-target sequence(s) (less than 90% homology to non-targets is recommended). We have identified the following useful guidelines for designing probes with the desired characteristics.
> First, probes should be positioned so as to minimize the stability of the probe:nontarget nucleic acid hybrid. This may be accomplished by minimizing the length of perfect complementarity to non-target organisms, avoiding G and C rich regions of homology to

> non-target sequences, and by positioning the probe to span as many destabilizing mismatches as possible (for example, dG:rU base pairs are less destabilizing than some others). Second, the stability of the probe:target nucleic acid hybrid should be maximized. This may be accomplished by avoiding long A and T rich sequences, by terminating the hybrids with G:C base pairs and by designing the probe with an appropriate Tm. The beginning and end points of the probe should be chosen so that the length and %G and %C result in a Tm about 2-10°C higher than the temperature at which the final assay will be performed. The importance and effect of various assay conditions will be explained further herein. Third, regions of the rRNA which are known to form strong structures inhibitory to hybridization are less preferred. Finally, probes with extensive self complementarity should be avoided."

Hogan teaches that "while oligonucleotide probes of different lengths and base composition may be used, oligonucleotide probes preferred in this invention are between about 15 and about 50 bases in length" (col. 10, lines l3-15). Oligonucleotides complementary to sequences adjacent to the probe regions were synthesized and used in the hybridization mix according to Hogan et al.,U.S. Pat. No. 5,030,557., filed Nov. 24, 1987, entitled "Means and Method for Enhancing Nucleic Acid Hybridization (the "helper " patent application). Hogan teaches that oligonucleotide probes may be labeled by any of several well known methods such as radioisotopes, non-radioactive reporting groups, non-isotopic materials such as fluorescent molecules (col. 10, lines 45-60). Hogan teaches that probes may be labeled using a variety of labels, as described within, and may be incorporated into diagnostic kits.

Buck expressly provides evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and

that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

However, it would have been prima facie obvious to include additional primers to detect the 5' region of the αs1 casein gene as taught by Schilds and include the primer of Koczan as well as generate a number of different primers for the use in the method of Schilds.

Designing primers and probes which are equivalents to those taught in the art is routine experimentation. The prior art teaches the parameters and objectives involved in the selection of oligonucleotides that function as probes and primers, see Hogan et al. Moreover there are many internet web sites that provide free downloadable software to aid in the selection of primers drawn from genetic data recorded in a spreadsheet. The prior art is replete with guidance and information necessary to permit the ordinary artisan in the field of nucleic acid detection to design primers and probes. As discussed above, the ordinary artisan would be motivated to have designed and tested new primers to obtain additional oligonucleotides that function to detect αs1 casein gene and identify oligonucleotides with improved properties. The ordinary artisan would have a reasonable expectation of success of obtaining additional probes from within the sequence and primers taught by Schild and Koczan . Thus, for the reasons provided above, the ordinary

artisan would have designed additional probes using the teachings in the art at the time the invention was made.

Conclusion

23. No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sarae Bausch whose telephone number is (571) 272-2912. The examiner can normally be reached on M-F 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866) 217-9197 (toll-free).

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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/Sarae Bausch/

Primary Examiner, Art Unit 1634